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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,790	11/17/2000	Rupert Schmidt-Ullrich	02940139AA	3995

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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,790	SCHMIDT-ULLRICH ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 Apr. 2003 & 15 Jun. 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-18,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 1-18 remain and new claims 34-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 18 Oct. 2002. Claims 34-35 are directed to non-elected Group I.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

The specific reference is present on page 1, but not in the first sentence as required. Lines 3-5 of page 1 should be deleted, and the text re-inserted following the section "Cross-reference to Related Applications."

Drawings

The drawings are objected to because the photographs in Figures 1A-B, 3A-C, and 4A-B are overexposed, and no detail is discernible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 23 is objected to because of the following informalities: recitation of "said expression cassette is Ad-EGFR-CD533" incorrectly conveys the physical relationship between the expression cassette and Ad-EGFR-CD533, which is a recombinant adenovirus that comprises the expression cassette. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 19, 21, 22, 24-32 remain rejected and claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action of 12/17/02. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 19 has been amended to indicate that the mutant EGFR is "dominant-negative." Claim 33 is similar to claim 19, but recites that the mutant EGFR is "carboxy terminal truncated." These amendments do not overcome the rejection. At issue is whether the specification adequately discloses a generic dominant negative mutant of EGFR other than those that are made so by carboxy terminal deletion, as exemplified by EGFR-CD533.

With respect to claim 33, the claim does not require that the mutant be dominant negative. However, the specification does not describe any C-terminal deleted EGFR mutants that are suitable for the invention other than those that are also dominant negative. Applicant has acknowledged in the reply of 4/2/03 (pages 4-5) that the purpose of the mutant EGFR is to

dimerize with the endogenous EGFR and prevent its normal action, i.e. it is a dominant negative EGFR. Sasaoka et al. (J. Biol. Chem. 271 (14): 8338-8344, 05 Apr. 1996) describes characterization of a carboxy-terminal deletion mutant of EGFR, Δ973-EGFR. Cells expressing this deletion mutant are still capable of EGF signaling and EGF-mediated proliferation despite the loss of the majority of autophosphorylation sites required to bind SH2-containing signaling proteins (see page 8338, col. 2 to page 8339, col. 1 for overview). This C-terminal deletion mutant is not dominant negative, and displays function similar to wild type EGFR, except that an alternate signaling pathway is used since the deletion prevents the normal pathway.

Applicant's arguments filed 4/2/03 have been fully considered but they are not persuasive. Applicant asserts with out supporting evidence that mutation of autophosphorylation sites within the cytoplasmic domain of EGFR by substitution or deletion would be expected to display properties similar to EGFR-CD533, and be dominant negative. However, Sasaoka discloses that EGFR mutants that have autophosphorylation sites replaced with alanine signal to the same extent as wild-type and a mutant having a C-terminal deletion of most of these sites (Δ973-EGFR) still mediates EGF-induced signaling and mitogenesis (see page 8338, col. 2 to page 8339, col. 1). Thus, Sasaoka contradicts Applicant's assertion.

Furthermore, the issue here is the sufficiency of the instant disclosure in describing a generic dominant negative mutant EGFR. Applicant has failed to indicate where the original specification teaches any such mutant EGFR as they propose in their reply. "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the

inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

The rejection would be overcome by limiting the claims to a carboxy-terminal deletion mutant EGFR that is dominant negative. The rejection of claims 20 and 23 is withdrawn, since these claims are (and were) limited to the dominant negative EGFR-CD533.

Claims 19-27 and 29-32 remain rejected and claim 33 is rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 12/17/02 because the specification, while being enabling either for radiosensitizing cancer cells generally *in vitro* or for radiosensitizing cancer cells *in vivo* specifically where the nucleic acid is administered directly to a tumor comprising cancer cells, does not reasonably provide enablement for other embodiments *in vivo* where the nucleic acid is not directly administered to a tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments filed 4/2/03 have been fully considered but they are not completely persuasive. Applicant's arguments that expression of a dominant-negative mutant of EGFR results in radiosensitization are convincing. As indicated in the re-statement of the rejection, the remaining issue is limited to whether the specification enables a broad method for radiosensitizing cancer cells *in vivo*. The claims broadly permit any route of delivery of the nucleic acid encoding the dominant negative or carboxy terminal truncated EGFR from systemic or remote delivery to direct injection or infusion into a target tumor. The specification does not enable all routes of administration.

Applicant alleges that the field of gene therapy has progressed significantly and that a skilled artisan would be aware of various alternatives for delivery of vectors. Applicant cites Gokhale, Printz and Xu in support of these assertions. However, none of these references were available when the instant invention was made (11/17/99), and do not show what one of skill in this art did or did not know. Also, Printz is not directed to delivery of gene vectors.

As to Applicant's assertion that gene therapy had progressed significantly or that one of skill in this art would be aware of various delivery routes, Rosenberg (Science 287: 1751, 10 March 2000) discloses a few months after the instant invention was made that "despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials." Most gene therapy trials had been directed to treatment of cancer. Applicant argues that delivery is not the key to the invention so longs as the vector is delivered to cancer cells. In order for one to practice the claimed invention for its intended purpose, as indicated by the preamble of claim 19 for example, the vector must be effectively delivered to cancer cells. The prior art had made clear that effective delivery was a serious problem that had not been solved. The instant specification does not teach how to solve that problem, other than by delivery of the vector directly to tumors, such as by injection or infusion of the nucleic acid into tumors.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The Bowers, Contessa, Dent, Mikkelson, Reardon, and Todd declarations under 37 CFR 1.132 filed 4/2/03 are sufficient to overcome the rejections under 35 USC 102 & 103 of claims 19-25 and 27-32 based upon Contessa et al. The Schmidt-Ullrich and Valerie declaration filed on 4/2/03 under 37 CFR 1.131 has been considered, but is moot.

Claims 19-22, 30, 32 and 33 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Reardon et al. (Oncogene 18(33): 4756-4766, 19 Aug. 1999).

See page 4757, for example. The claims do not require that the cancer cells be within a patient, as with claims 25-29, for example.

Reardon et al. is co-authored by inventors Schmidt-Ullrich and Valerie, and by Reardon, Contessa, Mikkelsen, Dent, and Amir. The declarations filed 4/2/03 by Reardon, Contessa, Mikkelsen, and Dent under 37 CFR 1.132 are sufficient to remove them as "inventors" of the claimed subject matter. The "inventive" entity of Reardon is deemed to be Amir, Schmidt-Ullrich and Valerie absent evidence to the contrary, which is a different "inventor" from that of the instant application.

Claims 19-22, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Zwick et al. (J. Biol. Chem. 272(40): 24767-24770, 03 Oct. 1997).

Zwick discloses a method of delivering to PC12 pheochromocytoma cells (a cancer cell line) a DNA comprising an expression cassette comprising an expressible nucleic acid encoding

EGFR-CD533 under control of a tet repressible promoter. See entire reference, especially page 24768, col. 2.

The rejected claims permit the cancer cells to be *in vitro*. The preamble of the claim indicates an intended use or a consequence of carrying out the recited method step, but otherwise places no material limitation on the method that would distinguish it from that disclosed in the reference. Since the prior art method is the same as that claimed, it is presumed that the cancer cells would be radiosensitized as an inherent consequence of expression of the dominant-negative EGFR.

Claims 19-22, 30, 32, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmidt-Ullrich et al. (Proc. Amer. Assoc. Cancer Res. Annu. Meeting 39: 78, Abst. 533, March 1998).

Schmidt-Ullrich discloses a method of delivering to breast carcinoma cells a DNA comprising an expression cassette comprising an expressible nucleic acid encoding EGFR-CD533 under control of a tet repressible promoter. Expression of EGFR-CD533 suppressed induction of proliferation by ionizing radiation.

The rejected claims permit the cancer cells to be *in vitro*. The preamble of the claim indicates an intended use or consequence of carrying out the recited method step, but otherwise places no material or procedural limitation on the method that would distinguish it from that disclosed in the reference. Since the prior art method is the same as that claimed, it is presumed that the cancer cells would be radiosensitized as an inherent consequence of expression of the dominant-negative EGFR.

Claims 19-22, 24, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Wagner et al. (Int. J. Cancer 68(6): 782-787, 11 Dec. 1996).

Wagner discloses a method of delivering to pancreatic cancer cells a DNA (plasmid vector) or RNA (retrovirus vector) comprising an expression cassette comprising an expressible nucleic acid encoding HER653, a dominant-negative, C-terminal truncated mutant of human EGFR, under control of a promoter. See entire reference, especially page 782, col. 2 to page 783, col. 1. The reference suggests that vectors expressing HER653 may be useful for treating pancreatic cancer and other malignancies that over-express EGFR (page 786, col. 2).

The rejected claims permit the cancer cells to be *in vitro*. The preamble of the claim indicates an intended use or consequence of carrying out the recited method step, but otherwise places no material or procedural limitation on the method that would distinguish it from that disclosed in the reference. Since the prior art method is the same as that claimed, it is presumed that the cancer cells would be radiosensitized as an inherent consequence of expression of the dominant-negative EGFR.

Claim Rejections - 35 USC § 103

Claims 19-25 and 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greene et al. (US 6,417,168) in view of Schmidt-Ullrich et al. (Proc. Amer. Assoc. Cancer Res. Annu. Meeting 39: 78, Abst. 533, March 1998); Wagner et al. (Int. J. Cancer 68(6): 782-787, 11 Dec. 1996); and Parker et al. (Proc. Amer. Assoc. Cancer Res. Annu. Meeting 38: 534, Abstr. 3581, April 1997).

Greene teaches methods of treating individuals who have erbB protein mediated tumors comprising the steps of administering to such individuals nucleic acid molecules that encode a protein that dimerizes with said erbB protein, such as erbBl (EGFR) and erbB2 (p185), and that is deficient in tyrosine kinase activity, and exposing said individual to a therapeutically effective amount of anti-cancer radiation (e.g. col. 4, line 10-30 and 56-67, col. 5, line 38-46, and col. 15, line 41-53), where the tumor cells include the tumors that comprise an EGFR species such as wild type or mutant EGFR (e.g. col. 6, line 8-16, pertaining to instant claim 32), such as malignant human gliomas (e.g. col. 11, line 50-61, and col. 19, 1ine13-15, pertaining to instant claim 31), or breast, ovarian, prostate or lung tumors (col. 20, lines 4-15); human mammary cell line HCII cells (e.g. col. 34, line 60-63, pertaining to instant claim 30). Preferably the dimerizing protein lacking tyrosine kinase activity is a truncated or mutated form of an erbB member or a chimera of parts of erbB members (e.g. col. 14, lines 12-26; col. 23, lines 5-40). Greene further teaches the nucleic acid molecules can be delivered in DNA form by viral vector delivery, e.g. adenoviral vector, in an expression cassette (e.g. col. 6, lines 37-40; col. 16, line 24-56; and col. 28, lines 10-32, pertaining to instant claims 21-22 and 29) or liposome mediated transfer (e.g. col. 17, line 4-22, pertaining to instant claim 29); or in RNA form by retrovirus delivery (e.g. col. 16, line 57-63, pertaining to instant claim 24), and suggest the delivery routes such as intratumoral, intravenous and subcutaneous administration (col. 17, line 38-44). Greene teaches that the method sensitizes radiation-resistant tumors to radiation by disrupting multimeric kinase protein ensembles, such as involving erbB members (col. 23, line 41 to col. 24, line 31). Furthermore, Greene teaches an example of a nucleic acid sequence encodes truncation species of rat p185 comprising either N-terminal or C-terminal deletions that dimerize with either human

p185 or human EGFR or a fusion protein comprising the EGFR extracellular domain (ectodomain) and p185 transmembrane domain, and which lack tyrosine kinase activity (e.g. cols. 6-7; col. 21, line 6-21) can be used for the treatment. Although Greene generally teaches using nucleic acids that encode truncated, kinase-deficient mutants of erbB family members, it does not explicitly teach to use a nucleic acid encoding dominant-negative, C-terminal truncation mutants of EGFR, such as EGFR-CD533 or HER653, for the treatment.

Schmidt-Ullrich disclosed that recombinant expression of a dominant-negative EGFR (EGFR-CD533) in breast cancer cells *in vitro* suppressed wild-type EGFR mediation of proliferation induced by ionizing radiation. Expression of the dominant-negative EGFR inhibited wild-type EGFR though protein-protein interaction with wild type EGFR and suppression of wild-type EGFR expression. The reference teaches that EGFR is a potential target of therapeutic intervention of ionizing radiation induced proliferation in cancer cells.

Wagner discloses that over expression of EGFR in a variety of tumors correlates with enhanced metastatic potential and aggressiveness, and that pancreatic tumor cell lines are known to overexpress EGFR and its ligands. The reference discloses that recombinant expression of a C-terminal truncated, dominant-negative mutant EGFR (HER653) in pancreatic tumor cells *in vitro* greatly inhibits their proliferation and enhances the cytotoxic effect of cisplatinum on these cells. The reference suggests that vectors expressing HER653 may be useful for treating pancreatic cancer and other malignancies that over-express EGFR. (See pages 782, 783, 785, 786, for example.)

Parker disclosed that expression of EGFR in human colon carcinoma (HCC) cells directly correlates with metastasis. Metastatic HCC cells were transfected with plasmid (DNA) or

retroviral (RNA) vectors expressing a dominant-negative, signaling-defective mutant of EGF-R, which resulted in a substantial inhibition of autophosphorylation of wild-type EGFR. The transfected HCC cells were implanted into the spleen of nude mice and examined for liver metastasis. Expression of the mutant EGFR greatly decreased the level of liver metastasis as compared to untransfected HCC cells.

One of skill in the art of tumor gene therapy would be motivated to use a vector encoding a C-terminal truncated, dominant negative mutant of EGFR, such as EGFR-CD533, in the treatment method taught by Greene with a reasonable expectation of success. C-terminal truncated, dominant-negative mutants of EGFR, such as EGFR-CD533, meet the requirements taught by Greene for a protein that dimerizes with an erbB protein, such as erbBl (EGFR) and erbB2 (p185), and is deficient in tyrosine kinase activity. Furthermore, Schmidt-Ullrich, Wagner, and Parker show that recombinant expression of a C-terminal truncated, dominant negative mutant of EGFR disrupts or inhibits the function of wild-type EGFR in promoting ionizing radiation induced proliferation and EGFR-mediated metastasis and aggressive growth of various types of tumor cells. Therefore, at the time the invention was made it would have been prima facie obvious to modify the teaching of Greene to use a nucleic acid encoding a C-terminal truncated, dominant negative mutant of EGFR, such as EGFR-CD533, for the treatment taught by Greene. Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe
Primary Examiner
Art Unit 1632